DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 23 1999

1527 '99 MAR 24 P1:37

Anthony G. Amitrano
Associate Head, Regulatory Affairs
SmithKline Beecham Consumer Healthcare
1500 Littleton Road
Parsippany, New Jersey 07054-3884

Re: Docket No. 81N-0033
Comment No. CP4

Dear Mr. Amitrano:

This is in response to your citizen petition requesting that the Food and Drug Administration (FDA) reopen the administrative record to include the combination of benzocaine and dyclonine hydrochloride (dyclonine) at therapeutic doses in the Agency's review of OTC oral health care drug products for the relief of oral discomfort. The petition also requests the Agency to allow interim marketing of a benzocaine-dyclonine combination product during its review of this class of drug products. The undated petition is filed as CP4 under Docket No. 81N-0033.

The Division of OTC Drug Products has reviewed the petition and other information and concludes that your requests cannot be granted at this time.

With respect to reopening the administrative record, we find that we could grant a future request to accept data on benzocaine and dyclonine and consider this combination of ingredients in the review of OTC drugs for relief of oral discomfort. However, full supporting data from well-controlled clinical trials will be required before the combination can be considered for inclusion in the monograph. Clinical studies must demonstrate that the combination of the two analgesic ingredients has some advantage over either ingredient used alone, and must provide assurance that the combination of ingredients is safe. Comparisons to benzocaine and phenol will not be adequate to demonstrate the safety and effectiveness of benzocaine and dyclonine.

As rationale for the benzocaine and dyclonine in combination, the petition cites the inclusion of benzocaine and phenol in the tentative final monograph (TFM) for OTC relief of oral discomfort drug products (56 FR 48302, September 24, 1991). The Agency proposed that the combinations of benzocaine with phenol and benzocaine with menthol could be placed in Category I. This determination was based upon the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) (44 FR 69768) regarding external analgesics, and upon safety data submitted to the Oral Cavity Panel for such combinations (OTC Volumes 130082 and 130020).

The Agency's combination policy in 21 CFR 330.10(a)(4)(iv), supplemented by the General Guidelines for OTC Drug Combination Products, September 1978, states that an OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as

81N-0033 LET 48

safe and effective when: (1) Each active ingredient makes a contribution to the claimed effect(s); (2) combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and (3) the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population. Further, paragraph 3 of the General Guidelines states that Category I ingredients from the same therapeutic category having the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. Nevertheless, they may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose.

The Topical Analgesic Panel placed benzocaine and dyclonine in the same subclass of external analgesic ingredients (44 FR 69768 at 69786). Phenol and menthol were placed in a different subclass. A majority of the Panel believed that the combination of ingredients from different chemical and pharmacological subclasses allowed for a selection of ingredients working on different receptor sites to provide variegated responses and the Agency accepted the conclusions of the Panel majority in the tentative final monograph for OTC external analgesic drug products (48 FR 5852).

Because dyclonine hydrochloride and benzocaine are from the same pharmacotherapeutic subclass, have a similar mechanism of action, and act at the same receptor sites, data from clinical trials are needed to demonstrate that the proposed combination meets the Agency's combination policy in all respects.

You stated in your letter that the proposed combination was compared to two single active marketed products, Chloraseptic® (containing benzocaine 6 mg and menthol 10 mg) and Maximum Strength Sucrets® Lozenges (containing dyclonine 3.0 mg), and that the data revealed that the buccal irritation produced in the new combination was no greater than that observed with the branded names. However, no human data were cited to support your position.

The Agency concludes that, to be included in the review of OTC drug products for relief of oral discomfort, full supporting human clinical data will be required for the proposed combination of benzocaine and dyclonine. Clinical trials should be designed to demonstrate that there is some advantage over the single ingredients in terms of enhanced effectiveness (i.e., equal to or better than each of the ingredients used alone at its therapeutic dose) safety, patient acceptance, and/or quality of formulation. We suggest that you submit a protocol for these trials for our review before beginning any studies. The completed studies can subsequently be submitted by a citizen petition and the administrative record can be reopened at that time.

With respect to your request to allow interim marketing of this combination during the review, our position has not changed from what we stated in our letter dated November 3, 1994 (copy enclosed). The combination of benzocaine and dyclonine was not evaluated by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products and is not included in the tentative final monograph for OTC oral health care drug products. Furthermore, the Agency is not aware that such a combination drug product has ever been marketed. Accordingly, during the period that the combination is under agency review, it may not be marketed except under an approved new drug application.

We intend to recommend that the Associate Commissioner for Regulatory Affairs respond to your petition in the above manner. Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket and citizen petition numbers shown that the beginning of this letter, to the Dockets Management Branch, (HFA-305), Food and Drug Administration, Room 1061, 5630 Fishers Lane, Rockville, Maryland 20852.

We hope this information will be helpful.

Sincerely yours,

Debra L. Bowen, M.D.
Acting Director
Division of OTC Drug Evaluation
Office of Drug Evaluation V
Center for Drug Evaluation and Research

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 23 1999

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 81N-0033

TO: Dockets Management Branch, HFA-305

☒ The attached material should be placed on public display under the above referenced Docket No.

☒ This material should be cross-referenced to Comment No. CP 4.

Debra L. Bowen, M.D.

Attachment